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The Safety and Efficacy of Combination Therapy of Dapagliflozin and Metformin in Patient with Type 2 Diabetes Mellitus: A Review Study

Saif K. Alkhanferi[1,2,3], Khadeejah H. Alhuraiz[1,2,3], Hussein S. Alyami[1,2,3], Sultan L. Alenazi[1,2,4], Mohammed F. Aldhaban[1,2,4], Naif Alrowedann[1,2,4], Yazeed Y. Albedaiwi[1,2,3], Nawal Alnazawi[1,2,3], Abrar Bokhamseen[1,2,3], Fatimah A. Talaqof[1,2,3]

[1]King Abdulaziz Medical City, National Guard Health Affairs, Riyadh, Saudi Arabia
[2]King Abdullah International Medical Research Center, Riyadh, Saudi Arabia
[3]Imam Abdurrahman Bin Faisal Hospital, National Guard Health Affairs, Dammam, Saudi Arabia
[4]Qassim Primary Health Care Center, National Guard Health Affairs, Qassim, Saudi Arabia
Email: er.research.gate@gmail.com

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Abstract

Background: Sodium glucose co-transporter 2 (SGLT2) inhibitors are a new class that approved by FDA for patient with type 2 DM. Dapagliflozin alone or in combination therapy with metformin provided effective glycemic control and HbA_{1c} reduction, with minimal hypoglycemia and hypotension adverse effects. **Objective:** To evaluate the safety and efficacy of the combination therapy of dapagliflozin and metformin in type 2 diabetes mellitus patients. **Methods:** Research was conducted through MEDLINE and Embase databases in search of randomized controlled studies including dapagliflozin, sodium glucose co-transporter 2, metformin, and efficacy. **Results:** Forty seven articles were spotted, 3 randomized controlled studies were involved in this review. Dapagliflozin and metformin combination was found beneficial in HbA_{1c} reduction equal to 20.7% - 31.5% from the baseline compared to patients on metformin alone. 40.6% of patients on combination therapy achieved the ADA recommended reduction in HbA_{1c} to less than 7%. Moreover fasting plasma glucose level was reduced by 23.4 mg/dl from the baseline in the combination therapy compared to 5.9 mg/dl in metformin group. Body weight reduction was statistically significant ($P < 0.0001$) in the combination group. Moreover reduction in patient's waist circumference was observed to be greater in all combination groups compared to MET group. Mild intensity of adverse effects such as major hypoglycemia, hypotension, or incidence of electrolyte changes was perceived. Therapy discontinuation was less likely with combination group. While UTI and genital infection were observed at

higher extent in combination group than MET group. **Conclusion:** The combination therapy of dapagliflozin and metformin found to be safe and effective in type 2 diabetes mellitus management with minimal adverse effects.

Keywords

Dapagliflozin, Sodium Glucose Co-Transporter 2, SGLT2, Metformin, Efficacy

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by high fasting plasma glucose level (FPG ≥ 126 mg/dl) due to insufficient production (Type 1 DM, accounting for 5 - 10%) or poor effectiveness of insulin (Type 2 DM, accounting for 90% - 95%). Diagnostic tests for diabetes include the FPG test, glycosylated hemoglobin (HbA_{1c}) which gives a better estimation of plasma glucose in previous 3 months and good indicator of complication due to diabetes, and 2 hours after 75-g oral glucose tolerance (OGTT) test (Table 1). Obesity and sedentary lifestyle are risk factors for type 2 DM [1]. Uncontrolled hyperglycemia leads to microvascular complications such as retinopathy, nephropathy, and neuropathy and macrovascular complications such as cardiovascular, cerebrovascular, and peripheral arterial disease. Other complications include nervous system damage, dental disease, limb amputation, and ketoacidosis [2]. It is not surprising, therefore, that diabetes is a leading cause of morbidity and

Table 1. Summary ADA criteria for diagnosis and target goals of DM.

TEST	Pre-diabetes	Diagnosed	Target	COMMENTS
Glycosylated hemoglobin A1c (HbA_{1c})	5.7% - 6.4%	≥6.5	≤7%	• Shows the average level of glucose over the previous 3 months. • The A1C test should be performed using a method that is certified by the NGSP and standardized or traceable to the DCCT reference assay. • A1C levels may vary with patients' race/ethnicity
Fasting plasma glucose (FPG)	100 - 125 mg/dl (5.6mmol/L - 6.9 mmol/L)	≥126 mg/dl (7 mmol/L)	70 - 130 mg/dl (3.9 - 7.2 mmol/L)	• Patient should be fast for at least 8 hours before the test.
Oral glucose tolerance test (OGTT)	140 - 199 mg/dl (7.8 mmol/L - 11.0 mmol/L)	≥200 mg/dl (11.1 mmol/L)	180 mg/dl (10.0 mmol/L)	• Use to measure patient's ability to utilize glucose at certain time. • Patient should be fast to perform 2-hours after 75 gram of glucose drink. For pregnant women use 100 gram of glucose test. • Recommended in gestational diabetes patient.
Random plasma glucose	-	≥200 mg/dl (11.1 mmol/L)	-	• Perform at any time of the day.

NGSP: National Glycohemoglobin Standardization Program. DCCT: Diabetes Control and Complications Trial.

mortality [3]. In 2010, about 25 million people in the US were affected by DM and almost 80 million were diagnosed as pre-diabetic (**Table 1**) [3]. Motivation for controlling DM and discover new effective medication will help prospective patients (366 million) in 2030 [4].

The American Diabetes Association (ADA) recommends for lowering FPG and postprandial (OGTT) glucose levels (**Table 1**) for all diabetic patients. In addition, lower $HbA_{1c} \leq 7\%$ has been shown to reduce microvascular and macrovascular complications. Targeting HbA_{1c} to ≤6.5% in younger patients without a cardiovascular disease and therefore expected live longer may be treated more aggressively since they are less likely to have hypoglycemia, other adverse effects of treatment, and slower progression of the disease [2].

Type 2 DM is treated with lifestyle modifications (reduced intake of calories and fat, 7% of the body weight loss, and 150 minutes of physical activity per week) alone or in combination with oral antidiabetic medications (OADs). When OADs are indicated, metformin is the recommended by ADA because of its high efficacy in reducing HbA_{1c}, less risk of hypoglycemia, and its low cost compared to other OADs. If ADA goals are not achieved over 3 months by metformin, adding another class of OAD such as sulfonylurea, thiazolidinedione, Glucagon like peptide 1 receptor agonist, dipeptidyl peptidase-4 inhibitor, or even insulin injection is recommended by ADA. Combination therapy with different mechanisms of action is crucial to control patient hyperglycemia and reduce long term complications. Mechanism of action, effectiveness, safety, adverse reactions, tolerability, cost, and reduction of long term complications are strategies used for selection of add-on OADs. However, common limiting adverse effects of some OAD medications are weight gain and hypoglycemia with sulfonylurea and insulin, fluid retention and progression of heart failure with thiazolidinedione, and gastrointestinal side effects with alpha-glucosidase inhibitors [2] [5]. Thus, newer drugs are needed that may be effective in combination with metformin to achieve treatment goals with minimal adverse effects.

Sodium glucose co-transporter 2 (SGLT2) inhibitors are a novel class that approved for use in patient with type 2 DM. SGLT2 is a membrane transporter located in the proximal renal tubules responsible for 90% of the glucose reabsorption. Inhibition of SGLT2 will inhibit the reabsorption of glucose and thus increases glucose and sodium excretion in urine. As a result, plasma glucose levels decrease [6] [7]. Canagliflozin (Invokana®) was the first SGLT2 inhibitor drug approved (March 2013) to treat adults with type 2 DM. Although Canagliflozin is efficacious, high risk of urogenital tract infections and hyperkalemia are the most common limitations for wide spread use [8]. Dapagliflozin (Farxiga®) is also SGLT2 inhibitor approved in the US (January 2014). SGLT2 medications are independent of insulin hormone and can be used as a monotherapy or in combination with other OADs [9] [10]. The use of Dapagliflozin as a treatment for type 2 DM as monotherapy has been already reviewed [11] [12]. The purpose of this review was to investigate the safety and efficacy of Dapagliflozin in combination with metformin in type 2 DM patients.

2. Data Sources and Selection

A literature search was performed through MEDLINE and Embase. Keywords included Dapagliflozin, Sodium glucose co-transporter 2, SGLT2, Metformin, and Efficacy. The search was limited to English language, human, Randomized controlled trial, and clinical trials (phase 3 and phase 4). This yielded 9 articles in MEDLINE and 38 articles in Embase. Studies were excluded if they discussed SGLT2 drugs other than Dapagliflozin, were duplicated, or were published as systemic review articles or as conference abstract articles. Three studies that compared the efficacy of combination therapy of Dapagliflozin and metformin in patient with Type 2 Diabetes mellitus met our inclusion criteria and were therefore selected for this review (**Figure 1**).

3. Results

The efficacy and safety of Dapagliflozin (Farxiga®) and metformin (MET) combination in patients with type 2 DM who have inadequate glycemic control with metformin and have high baseline HbA_{1c} were evaluated in three different studies (**Table 2**). Bailey *et al.* published the results of the trial at the end of 24 weeks and 102 weeks of one study research [5] [13]. Two separate studies investigating two separate doses (5 mg and 10 mg) of Dapagliflozin were reported together in one article [14].

All these studies [5] [13] [14], had similar inclusion and exclusion criteria. Patients were included if they were aged ≥ 18 years, had type 2 diabetes, C-peptide concentration was ≥1 ng/ml, body-mass index (BMI) was ≤45 kg/m^2, and were administering metformin (≥1500 mg per day). Patients were excluded from the study if the serum creatinine was ≥1.5 mg/dl (for men) or ≥1.4 mg/dl (for women), urine albumin/creatinine ratio was >1800 mg/g, aspartate aminotransferase, alanine aminotransferase, or creatine kinase was greater than three times the upper limit of normal, or had symptoms of poorly controlled diabetes (polyuria and polydipsia with >10% weight loss during the 3 months before enrollment). Patients were also excluded if they suffered from clinically significant disease (renal, hepatic, hematological, oncology, endocrine, psychiatric, or rheumatic diseases), BP was ≥180/110mm Hg, had a recent (within 6 months) cardiovascular

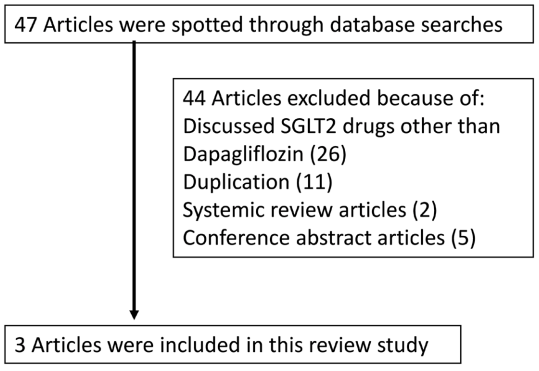

Figure 1. Summary of data sources and article selection.

Table 2. Summary of Dapagliflozin trials as a combination therapy with metformin.

Reference	Design (n)	Duration (week)	Primary outcome (s)	Interventions	Results	Safety outcome)
Bailey (2013)	MC, R, PC, DB, PGT (476)	102	HbA_{1c} changes from baseline at 78 weeks.	MET only MET + DAP • 2.5 mg • 5 mg • 10 mg	0.02% −0.48%* −0.58%* −0.78%*	• Three deaths reported, 2 in DAP 2.5 mg group (cardiac arrest and MI) and 1 in placebo group (lung cancer) • UTI incidence was higher in DAP 10 mg. • In general, renal impairment was observed to a great extent in DAP groups than placebo. • A significant beneficial reduction of blood pressure was observed in patients with hypertension with DAP groups.
Henry (2012)	MC, R, DB, ACS (598)	24	HbA_{1c} changes from baseline at 24 weeks.	• MET only • DAP 5 mg • DAP + MET	−1.35 −1.19 −2.05*	• No major hypoglycemia was observed in any groups. • Mild to moderate ADR among groups. • Diarrhea was more common in MET groups than DAP groups. • UTI was reported more frequently in DAP + MET groups. • Significant changes in the renal function were not detected. • A significant reduction of blood pressure was observed in patients with hypertension with DAP + MET groups.
Henry (2012)	MC, R, DB, ACS (638)	24	HbA_{1c} changes from baseline at 24 weeks.	• MET only • DAP 10 mg • DAP + MET	−1.44 −1.45 −1.98*	
Bailey (2010)	MC, R, PC, DB, PGT (546)	24	HbA_{1c} changes from baseline at 24 weeks.	MET only MET + DAP • 2.5 mg • 5 mg • 10 mg	−0.30% −0.67%* −0.70%* −0.84%*	• No major hypoglycemia was observed in any groups. • Discontinuation of therapy was less frequent in the DAP groups. • UTI was observed in all groups, but was higher in DAP groups. • No major differences were observed in serum electrolytes, renal function, and lipid profiles. • A significant reduction of blood pressure was observed in patients with hypertension with DAP groups.

MC = Multicenter; R= randomized; PR = placebo-controlled; DB = double bind; PGT = Parallel-group trial; ACS = active-controlled studies, DAP = Dapagliflozin, MET = Metformin, ADR = adverse reaction, UT I = urinary tract infection. *P value < 0.001 as compared to either baseline or placebo (MET).

event or diagnosed with congestive heart failure class III or IV, based on New York Heart Association.

All primary and secondary endpoints were same in all trials. The primary endpoint was to observe the reduction of HbA_{1c} from the baseline at the end of the study whereas secondary endpoints included changes in FPG, total body weight, and adverse effects such as hypoglycemia, hypotension, UTI and genital infections, and abnormalities in electrolytes and kidney function.

Bailey *et al.* conducted a phase 3 randomized, multicenter, double-blind, and placebo-controlled trial, and published their finding at two different time points

(24 weeks and 102 weeks (78 weeks extension of the first trial)). Of the 546 patients who were included at the end of 24 weeks, only 476 patients continued the study up to 102 weeks. [5] [13]. HbA_{1c} level of those patients were between 7% - 10%. Each patient received 2-weeks of placebo single blind to assess patient compliance by Interactive voice response system (IVRS). Medication compliant patients were randomly assigned to one of the four groups of the study, metformin alone (MET) group or combination of metformin + Dapagliflozin (MET + DAP), 2.5 mg, 5 mg, and 10 mg groups (**Table 2**).

FPG was assessed from week 4 to the end of the study to determine if patients needed a rescue medication (Pioglitazone or Acarbose). Rescue medication was administered if FPG higher than the predetermined levels. Patients also received diet and exercise counseling throughout the study.

The reduction in the HbA_{1c} was significantly higher compared to baseline in the combination (MET + DAP) groups than metformin alone (MET) group at the end of 24 weeks and 102 weeks (**Table 2**). Moreover, at the end of 24 weeks, 33% - 40.6% of patients in the MET + DAP groups achieved the ADA recommended reduction in HbA_{1c} to less than 7% compared to 25.9% of patients in MET group. However, at the end of 102 weeks, these percentages dropped to 20.7% - 31.5% of patients in the MET + DAP groups compared to 15.4% of patients in MET group.

A significant reduction in number of patients with $HbA_{1c} \geq 9\%$ at baseline was observed in MET + DAP 5 mg and 10 mg groups ($P < 0.03$) but not in MET + DAP 2.5 mg group at week 24. Moreover, patients with MET + DAP 10 mg group showed a greater reduction in patients' HbA_{1c} to $\leq 6.5\%$ ($P < 0.02$). These end points were not reported in 102 weeks because the patients HbA_{1c} baseline at the beginning of the extension period (78 weeks) was less than 9%. However, it was surprising to note that at 102 weeks study, reduction of $HbA_{1c} \leq 6.5\%$ was not reported.

A reduction in patients' FPG was observed from the baseline at the end of first week and this reduction was statistically significant only in MET + DAP 5 mg and 10 mg groups ($P < 0.001$). At week 24, FPG was reduced by 17.8 - 23.4 mg/dl from the baseline in all MET + DAP groups and by 5.9 mg/dl in MET alone group. FPG also was observed to reduce by 19.3 to 26.5 mg/dl from the baseline in all MET + DAP groups at the end of week 102 while the reduction in FPG was 10.5 mg/dl in MET alone group. Moreover, all study groups except MET +DAP 2.5 mg group showed a significant reduction in patients FPG at the end of the study ($P < 0.002$).

A continuous reduction in patient body weight (−2.2 kg to −3.0 kg) was observed from week 1 up to week 24 in MET + DAP groups. This reduction of patient body weight from the baseline was statistically significant in MET + DAP groups as compared to MET alone group ($P < 0.0001$) at week 24 and week 102. However, a small increase in body weight from week 24 to week 102 was observed. At the end of the 24 weeks, the reduction of body weight ≥ 5% was sig-

nificantly higher in MET + DAP groups (18.1%, 19.5%, 22.1% in 2.5 mg, 5 mg, 10 mg, respectively) as compared to MET group. Moreover, the reduction in patient's waist circumference was observed to a greater extent in all MET + DAP groups (−1.7 cm, −2.7 cm, and −2.5 cm in 2.5 mg, 5 mg, 10 mg, respectively) compared to −1.3 cm in the MET group. However, it was surprising to note that the authors did not report the change in waist circumference at the week 102 as they did at the end of week 24.

Adverse effects leading to therapy discontinuation were less likely with patients in MET + DAP groups as compared to MET alone group. Moreover, the incidence of high urinary glucose/creatinine ratio was observed to a greater extent in patients in MET + DAP groups. This elevation was dose dependent. Minimal differences existed between all groups of the study regarding major hypoglycemia, hypotension, or incidence of electrolyte changes. Changes in the sodium and potassium levels were transient but not clinical relevant in any study group at any point.

UTI was observed to a greater extent in MET + DAP 10 mg group. Genital infections occurred more frequently in all MET + DAP groups (8% to 14.6%) than MET group (5%). UTI and genital infections were observed at similar extent in both sexes at week 24 while women showed more frequent UTI and genital infections at the end of the 102 weeks. The tests for renal, hepatic and lipid functions did not show any significant differences between any groups at week 24. However, patients in MET + DAP groups at week 102 showed a higher incidence of renal failure. But the incidence in patients in MET + DAP 10 mg group and MET alone group was similar. Moreover, MET + DAP groups showed a robust reduction in the serum uric acid at week 24 and 102 than MET alone group. The reduction of blood pressure (systolic and diastolic) from the baseline was observed more frequently in MET + DAP groups at week 24, but minimal changes were observed at week 102. Reduction of blood pressure was not associated with orthostatic hypotension. A robust, reduction in blood pressure of patients with hypertension (>130/80) at baseline was observed at the end of 24 weeks in all MET + DAP groups (29.5% - 37.5%). Three deaths were reported during the extension study (78 weeks). Two deaths occurred in MET + DAP 2.5 mg group (cardiopulmonary arrest and myocardial infarction) and one death occurred in MET alone group (malignant lung neoplasm). Fractures also were reported in all groups but noticed to be at higher extent in patients in DAP + MET 10 mg group.

Henry *et al.* [14] performed two randomized, multicenter, double-blind, three arms, active controlled, 24 weeks studies (study 1 and study 2). Study 1 included 598 patients, distributed as 201, 203, and 194 patients in MET_{XR} group, MET_{XR} + DAP 5 mg group, and DAP 5 mg group respectively. Study 2 included 638 patients, distributed as 208, 219, and 211 patients in MET_{XR} group, MET_{XR} + DAP 10 mg group, and DAP 10 mg group respectively. In addition to inclusion and exclusion criteria mentioned above, patients who had HbA_{1c} 7.5% - 12% were

included while patients who had a history of diabetes insipidus were excluded from studies. Study 2 tested non inferiority of DAP 10 mg to MET_{XR} for changes in HbA_{1c} (0.35% margin) and FPG (14.96 mg/dl margin).

All patients received one week of placebo single blind to assess patient compliance. Patients who were determined to be medication complaint by IVRS were randomly assigned into one of the three groups of the studies. In addition to the treatment options, all patients received diet and exercise counseling. Patients were also assessed for uncontrolled FPG level from week 6 to determine if patient needed a rescue medication (Pioglitazone, Sitagliptin, or Acarbose).

Both studies (study 1 and study 2) showed a statistically significant reduction of HbA_{1c} in the combination therapy (MET_{XR} + DAP 5 mg and 10 mg) compared to either MET_{XR} alone or DAP alone groups ($P < 0.0001$). Moreover, reduction of HbA_{1c} less than 7% as ADA recommended was significant in combination therapy groups compared to either of the monotherapy groups ($P < 0.02$). The reduction in the number of patients with baseline $HbA_{1c} \geq 9\%$ also was significant to a greater extent in the combination therapy groups compared to the monotherapy groups ($P < 0.02$). However, MET_{XR} + DAP 5 mg group showed a greater reduction in patients $HbA_{1c} \geq 9\%$ at baseline than MET_{XR} + DAP 10 mg group when compared to either of the monotherapy groups. Additionally, both studies showed a significant reduction in FPG in combination therapy compared to either of the monotherapy ($P < 0.0001$). Reduction of patients body weight also was statistically significant in both combination therapy compared only to MET alone group ($P < 0.0001$).

At the end of the study 2, data showed a non-inferiority of DAP 10 mg group alone in HbA_{1c} reduction, superiority for reduction of FPG, and significant reduction in patient body weight when compared to MET_{XR} alone group.

Mild to moderate intensity of adverse effects were observed throughout the studies. DAP 5 mg and 10 mg as monotherapy or in combination showed less discontinuation from treatment groups and lesser need to add rescue medication to control high FPG compared to MET_{XR} alone group. However, patients who received MET_{XR} (combination or alone) showed more frequent diarrhea and nausea (7%- 9.6%) than patients in DAP 5 mg or 10 mg groups (2.7% - 3.9%). UTI and genital infections were observed more frequently with patients in DAP 5 mg and 10 mg groups (combination or monotherapy) than MET_{XR} groups. Moreover, UTI and genital infections were observed more commonly in women than men. This was in agreement with the finding of previous studies [5] [13]. All study groups except MET_{XR} group showed a robust reduction in patient serum uric acid level. Reduction of blood pressure was observed in patients in DAP 5 mg and 10 mg (monotherapy or in combination therapy) to a greater extent than MET_{XR} groups.

The strengths of all studies include a randomized, multicenter, and double-blind design, and the fact that they were sufficiently powered studies. Since metformin is contraindicated in patients who have high serum creatinine (1.5 mg/dl for men and 1.4 mg/dl for women), excluding these patients is important to avoid

accumulation of metformin. This accumulation of the drug may lead to serious adverse effects such as lactic acidosis which is disturbed plasma electrolytes and lead to tissue hypoxia. Some of the limitations of these studies are using interactive voice response system (IVRS) for determining patient compliance, which may introduce patient bias in different ways. Some patient may be pretend medication compliance or miss understanding the meaning of compliance when they response to the IVRS. Patients with clinically significant diseases such as hepatic or renal impairment, HbA_{1c} more than 10%, or C-peptide concentration less than 1 ng/ml also were excluded, which may limit the extrapolation of safety and efficacy finding of these studies to those populations. Those patients who are excluded because of the previous criteria may be form the majority of elderly patients with multi diseases. Moreover, all these studies were funded by the companies making Dapagliflozin (Farxiga®) which may introduce bias. In addition to the above limitations, discontinuing the follow up patients with $HbA_{1c} \leq$ 6.5% in the 102 weeks study was surprising and limiting the future adverse effect such hypoglycemia predication.

4. Discussion

Dapagliflozin pharmacological mechanism of action is inhibition of sodium-glucose cotransporter 2 (SGLT2), found in the proximal renal tubules, which is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and thereby promotes urinary glucose excretion [9]. Metformin acts through decreasing hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization [15].

Results from all 3 studies reviewed, indicate that combination of metformin plus Dapagliflozin is effective in reducing of HbA_{1c}, increasing the proportion of patients achieving target HbA_{1c} levels, and reducing FPG when compared to either metformin or Dapagliflozin alone. A significant reduction in HbA_{1c} (−0.48% to −0.78%) was achieved in all patients who had HbA_{1c} more than 7% at the beginning of the studies. This reduction in HbA_{1c} is dose related and can be as much as 0.9% with 50 mg dose of Dapagliflozin [12]. The reduction in HbA_{1c} (>9% at baseline) observed at higher extent with all metformin plus Dapagliflozin groups, however, metformin plus Dapagliflozin 5 mg showed more reduction than monotherapy and metformin plus Dapagliflozin 10 mg [13] [14]. Reduction of HbA_{1c} showed beneficial effects more than reducing cardiovascular risks in many patients [2]. FPG was significantly reduced in all 3 studies (−17.8 to −61 mg/dl) and this reduction was dose related as observed in other study [12].

Dapagliflozin (Farxiga©) is a selective SGLT2 inhibitor approved to manage patients with type 2 DM. Blocking SGLT2 in the proximal renal tubules increase glucose and sodium excretion in the urine and reduce hyperglycemia [9]. Dapagliflozin has several advantages over current available OADs. For example, unlike other OADs, the action of Dapagliflozin is insulin independent. Some

other OADs such as sulfonylurea and Glucagon like peptide 1 agonists need enough insulin concentration to present in patient's blood to be effective. However, the present studies included patients who had C-peptide concentration ≥ 1 ng/ml. Dapagliflozin efficacy should be assessed in patients with very low insulin production, C-peptide concentration less than 1 ng/ml. Since, serum sodium and potassium levels were normally distributed even when Dapagliflozin facilitated the excretion of sodium in the urine. Unlike canagliflozin, Dapagliflozin does not show any clinical changes in serum potassium level. Adding Dapagliflozin to metformin considered as safe and effective [5] [12] [13] [14].

After few weeks of significant body weight reduction were observed in the beginning of all studies, the body weight reduction was less extent at the end of all studies. One study measured the amount of glucose (calories) excreted by patients who used Dapagliflozin and it found to be arranged from 50 - 85 gram per day and that may explained the slowdown in the weight reduction throughout and at the end of the studies [12]. Moreover, the reduction in patients' body weight may be related to lose fluid due to the osmotic diuretic effect of Dapagliflozin [12] [16]. Losing both glucose and fluid in patients' urine are the best explanation for weight reduction at these studies. Further investigation should be done to get a full understanding for patient's weight changes with Dapagliflozin. Reduction of patients' body weight ≥ 7% is recommended by ADA to prevent or delay type 2 DM [2]. Dapagliflozin as monotherapy or in combination with metformin achieved > 5% reduction in body weight [5] [12]. Moreover, metformin plus Dapagliflozin in Bailey *et al.* showed a reduction in waist circumference of patients at 24 weeks which is a good indication of losing fat from abdominal area. However, the authors did not report the reduction in the waist circumference at end of 102 weeks. This is needed to fully understand patient body weight changes and long term efficacy [5] [14] [17].

Fewer adverse effects with Dapagliflozin were noticed and it was well tolerated. Major hypoglycemia does not appear to be a serious adverse effect with Dapagliflozin as monotherapy [12], or in combination [5] [13] [14]. One trial compared combination of Dapagliflozin with Pioglitazone to Pioglitazone alone, found no major incidence of hypoglycemia for almost one year with Dapagliflozin [18]. Moreover, Comparing Dapagliflozin to Glipizide in a study with patient who were already on metformin, found Dapagliflozin had 10 fold lesser incidences of hypoglycemia and less treatment discontinuation compared to Glipizide group [16]. All these studies showed neither major incidences nor treatment discontinuation because of hypoglycemia with Dapagliflozin and that may be related to the Dapagliflozin mechanism and less aggressive of losing glucose in the urine.

The reduction in the blood pressure in patients who already had high blood pressure (>130/80mm Hg) was observed in the first 24 weeks of both studies and that does not increased chance of hypotension or orthostatic hypotension with patients. This reduction was observed in either Dapagliflozin alone or in combination at short period of the study with no clear relation to dose [5] [12] [13]

[14] [16]. This reduction in blood pressure is suggested to be related to osmotic diuretic effect of Dapagliflozin as well as body weight loss. On the other hand, a recent meta-analysis study stated that bias in the studies which showed a great reduction in the blood pressure with patients on Dapagliflozin compared to placebo or other OADs was high [10]. Blood pressure reduction may be beneficial in patients who are at high risk of stroke and heart failure with type 2 DM. Other adverse effects must be also considered with patients who are using Dapagliflozin alone or in combination are UTI and genital infections which were always higher and especially with women than men. Usually, infections were treated and resolved with standard treatment of antibiotics and rarely lead to discontinuation from studies. Results from different studies manifested that UTI and genital infections were higher than placebo or other OADs and seen greater in high doses of Dapagliflozin, dose related [12] [18] [19].

Serum uric acid was also significantly reduce with any Dapagliflozin dose or in combination and that appeared not dose related [12] [13] [14]. A reason of this effect is unclear but the level of serum uric acid returned toward baseline after Dapagliflozin discontinued [12]. Thus, this reduction in serum uric acid may be beneficial in patient with type 2 DM who has gout or hyperuricemia.

5. Conclusion

Dapagliflozin is SGLT2 inhibitor indicated to be used for type 2 diabetes mellitus in adult patients. This review study establishes that combination therapy of dapagliflozin and metformin is safe and effective in type 2 diabetes mellitus with minimal adverse effects.

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The authors listed in the byline are the only investigators responsible for this review article. This review was performed through electronic medical search engines. This review article has been not presented at any conference or meeting.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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